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CSF β-Amyloid 1-42 Predicts Progression to Cognitive Impairment in Newly Diagnosed Parkinson Disease

Mark Terrelonge Jr.[1] · **Karen S. Marder**[1] · **Daniel Weintraub**[2,3] · **Roy N. Alcalay**[1]

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Abstract Low CSF β-amyloid 1-42 has been associated with cognitive decline in advanced Parkinson's disease; data from a single cohort suggest β-amyloid 1-42 may be an early marker of cognitive impairment. Newly diagnosed Parkinson's participants (mean duration, 6.9 months) in the Parkinson's Progression Markers Initiative (n = 341) were assessed at baseline (untreated state) and followed for 2 years. CSF β-amyloid 1-42, α-synuclein, total tau, and tau phosphorylated at threonine 181 were collected at baseline. Participants were classified as having cognitive impairment (CI) if scores on two of six cognitive tests were 1.5 standard deviations below the standardized mean based on published norms in healthy controls. Multivariable regression analyses were used to determine the association between baseline CSF markers with cognitive impairment, defined by neuropsychological testing performance at 2-year follow-up. Fifty-five participants (16.1 %) had CI at baseline and were not included in further analyses. Thirty-seven of the 286 participants without CI at baseline (12.9 %) developed CI at 2 years. Participants with CI at 2 years had significantly lower mean baseline CSF β-amyloid 1-42 levels than non-CI participants (343.8 vs. 380.4 pg/mL, $p < 0.01$); no significant difference was seen for α-synuclein, T-tau, or P-tau 181. In a regression model of 286 participants without baseline CI adjusted for age, gender, disease duration, education, motor severity, and depression status, lower baseline β-amyloid 1-42 levels were associated with higher odds of CI at 2 years. ($OR_{10pg/mL}$ = 1.04, 95 % CI 1.01–1.08, $p < 0.05$). CSF β-amyloid 1-42 level at disease onset is an independent predictor of cognitive impairment in early Parkinson's disease.

Keywords CSF β-amyloid 1-42 · Cognitive impairment · Parkinson's disease · PPMI

Introduction

Up to 80 % of Parkinson disease (PD) patients develop dementia during the course of their illness [1]. Several baseline factors have been associated with more rapid cognitive decline in PD including advanced age at time of diagnosis, male gender, and education level [2]. The degenerative process may begin years before the first signs of cognitive impairment or dementia become apparent in both Alzheimer's disease (AD) and PD, and these changes may be reflected in CSF marker profile [3, 4]. Additionally, evidence has shown that lower CSF levels of β-amyloid predict faster cognitive decline among PD patients [5–7]. A study from the Norwegian ParkWest project, a population-based cohort study of newly diagnosed PD patients (mean disease duration of 2.2 years), found that CSF β-amyloid 1-42 (Aβ1-42) was associated with memory decline at the time of patient diagnosis [8]. Later analysis from the same cohort found that low CSF Aβ1-42 at baseline was associated with early dementia associated with PD (median time to dementia: 4.3 years) [9].

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✉ Roy N. Alcalay
RNA2104@COLUMBIA.EDU

[1] Department of Neurology, Columbia University, 710 W 168th St, New York, NY 10032, USA

[2] Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

[3] Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA

The Parkinson's Progression Markers Initiative (PPMI) is an international, multicenter prospective study following PD cases and controls with baseline CSF sampling and biannual neurological and cognitive evaluations [10]. A previous cross-sectional design study using partial PPMI data showed slight but significantly lower levels of CSF Aβ1-42, α-synuclein (α-syn), total tau (T-tau), and tau phosphorylated at threonine 181 (P-tau$_{181}$) in PD compared with healthy controls, with Aβ1-42 and P-tau$_{181}$ remaining lower than healthy control data after controlling for age, gender, and education [11]. We examined whether CSF concentration of Aβ1-42, α-syn, T-tau, and P-tau$_{181}$ at baseline predicts diagnosis of cognitive impairment at 2-year follow-up among newly diagnosed, drug-naïve PD patients without cognitive impairment.

Methods

Participants

Data were obtained from the PPMI database (www.ppmi-info.org/data) on August 10, 2015 [10]. Participants were included in this PD cohort if they enrolled in the study within 2 years of diagnosis and were not expected to require PD medication within 6 months of their baseline evaluation. Participants were excluded if they had a clinical diagnosis of dementia, were unable to participate in lumbar puncture, or had MRI evidence of another clinically significant neurological disorder. Scans without evidence for dopaminergic deficit (SWEDD) participants and control participants were not included in this study.

Individuals from the PD cohort who had 2 years of follow-up were included in the analysis. At the time of data acquisition, 341 PD participants (of original 406 with baseline data) had completed 2 years of study follow-up. Written informed consent was obtained from all participants, and all PPMI sites received approval from their respective ethics committee on human experimentation prior to study initiation.

Assessments

The annual assessment included six cognitive tests, which can be divided into four cognitive domains: memory (Hopkins Verbal Learning Test-Revised [HVLT-R] Recall, HVLT-R Recognition Discrimination) [12], visuospatial (Judgment of Line Orientation [JOLO]) [13], working memory-executive function (Letter Number Sequencing [LNS], Semantic Fluency) [14, 15], and attention-processing speed (Symbol Digit Modalities Test [SDMT]) [16]. Cognitive impairment was defined as having at least 2 test scores (of six; irrespective of test domain) greater than 1.5 standard deviation below the age- and education-standardized mean score based on published norms in healthy controls [17].

CSF Analysis

CSF samples were collected from all participants enrolled in the study at baseline including Aβ1-42, α-syn, T-tau, and P-tau$_{181}$. Additional information on how CSF samples were collected and analyzed was previously reported [11].

Statistical Analysis

Data were analyzed using SAS v 9.3. Participants with baseline cognitive impairment by the aforementioned definition were not included in future analyses. Baseline demographics (age, gender, PD duration from diagnosis, education, and 15-item Geriatric Depression Scale [GDS-15]), disease characteristics (Movement Disorder Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] motor score part 3, MDS-UPDRS part 1 Cognitive Impairment self-report at baseline, and MDS-UPDRS part 1 Cognitive Impairment self-report at 2 years), and baseline CSF marker levels and their ratios (α-syn/T-tau, T-tau/Aβ1-42, P-tau$_{181}$/Aβ1-42, P-tau$_{181}$/T-tau) were compared between participants with and without cognitive impairment (CI) at 2-year follow-up using either the Student t test or the chi-square test. Non-normal data were compared using the Wilcoxon rank sum test. Multivariable logistic regression was used to determine the association of baseline CSF measures and their ratios to CI at 2 years. The adjusted model included baseline age, gender, disease duration, education, MDS-UPDRS part 3 motor score, and Geriatric Depression Scale score. Significance level for all non-ratio tests was set at $p < 0.05$ (2-tailed test). Adjustment for multiple comparisons was used for all ratio tests with a Bonferroni-Holm correction.

Results

Participant Characteristics

Two-year follow-up data was available for 341 participants out of 406 assessed at baseline. There were no significant differences in baseline characteristics or biomarker profiles between those with 2 years of follow-up and those without 2 years of follow-up (Supplemental Table 1). Fifty-five participants had CI at baseline (16.1 %) and were not included in future analyses. Those with CI at baseline had greater motor impairment reflected by higher MDS-UPDRS motor scores (24.6 vs. 20.3, $p < 0.01$), had higher scores on depression rating scale (5.7 vs. 5.2, $p = 0.04$), and had a higher proportion of self-reported cognitive decline at baseline (43.6 vs. 23.4 %, $p < 0.01$) (Supplemental Table 2).

Of the 286 remaining participants without CI at baseline, 37 (12.9 %) developed CI by year 2. Demographics and disease characteristics were similar between those with and

without CI at 2 years (Table 1). Of note, in this cohort baseline self-reported cognitive changes on the MDS-UPDRS were not associated with later development of CI; however, at year 2 evaluation, those with CI were more likely to report cognitive changes during that evaluation (Table 1).

CSF Markers as Predictor of CI

Participants with CI at 2 years had significantly lower mean baseline CSF Aβ1-42 levels than those who did not (343.8 vs. 380.4 pg/mL, $p < 0.01$). No significant differences in CSF level were noted for α-syn, T-tau, or P-tau$_{181}$. Significant differences were not noted in the ratio of CSF T-tau/Aβ1-42, T-tau/α-syn, CSF P-tau$_{1181}$/Aβ1-42, or P-tau$_{181}$/T-tau (Table 1).

Logistic regression was used to test whether baseline CSF markers could predict CI at 2 years, adjusting for baseline demographic characteristics (Table 2). After adjustment for age, education, disease duration, gender, MDS-UPDRS motor score, and Geriatric Depression Score, CSF Aβ1-42 still predicted CI at 2 years. α-syn, T-tau, and P-tau$_{181}$ were not predictive of CI at 2 years in the univariate or multivariable models. CSF ratios of α-syn/T-tau, T-tau/Aβ1-42, P-tau-181/Aβ1-42, and P-tau-181/total tau were also not associated with CI at 2 years in multivariable models.

Discussion

In the present study of a medication-naïve PD cohort with 2 years follow-up, we found that lower baseline CSF Aβ1-42 was associated with higher odds of having CI after 2 years of follow-up after adjusting for baseline demographic characteristics. To our knowledge, this is the first study to demonstrate an association between lower baseline CSF Aβ1-42 levels in medication-naïve newly diagnosed PD cases without cognitive impairment and later development of CI as defined

Table 1 Comparison of demographics and Parkinson's disease characteristics between participants with and without cognitive impairment at 2 years

Baseline (year 0)			
Baseline characteristics	No cognitive impairment at 2 years ($N = 249$)	Cognitive impairment at 2 years ($N = 37$)	p value
Gender (% male)	161 (64.7 %)	26 (70.3 %)	0.44
Age (years)	60.6	61.8	0.48
Age at disease onset (years)	60.0	61.2	0.48
Disease duration (months)	6.9	7.7	0.51
Education (years)	15.8	15.3	0.26
Movement Disorders Society-Unified Parkinson's Disease Rating Scale Motor Score	8.7	9.8	0.23
Geriatric Depression Scale Score	5.2	4.9	0.11
Self-reported Cognitive changes at baseline on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale[a]	59 (23.7 %)	8 (21.6 %)	0.96
CSF Aβ1-42 levels pg/mL	380.4	343.8	<0.01
CSF alpha-synuclein pg/mL	1897.3	1689.2	0.14
CSF total tau pg/mL	44.1	40.9	0.29
CSF phosphorylated tau-181 pg/mL	16.2	14.9	0.31
CSF alpha-synuclein/total tau	44.9	42.3	0.28
CSF total tau/Aβ1-42	0.12	0.13	0.63
CSF phosphorylated tau-181/Aβ1-42	0.04	0.04	0.88
CSF phosphorylated tau-181/total tau	0.39	0.38	0.83
Year 2			
	No cognitive impairment at 2 years ($N = 249$)	Cognitive impairment at 2 years ($N = 37$)	p value
Self-reported cognitive changes at 2-year follow-up on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale[a]	76 (30.5 %)	19 (51.4 %)	<0.01

Values denote means or N (percentage) unless otherwise indicated. p values computed using Student's t test, Wilcoxon rank sum test, or χ^2 test as appropriate

[a] Self report cognitive change was defined as a score higher than 0 on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale cognition question

Table 2 The association between cognitive impairment (outcome) and CSF markers (predictors) in univariate and multivariable regression models [OR for decrease in CSF marker levels]

	Univariable analysis			Multivariable analysis[a]		
CSF markers	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Aβ1-42$_{10\ pg/mL}$	0.96	(0.92, 0.99)	0.03	0.96	(0.92, 0.99)	0.04
α-synuclein$_{10\ pg/mL}$	0.99	(0.99, 1.00)	0.13	0.99	(0.99, 1.00)	0.14
total tau$_{10\ pg/mL}$	0.89	(0.70, 1.11)	0.27	0.88	(0.69, 1.11)	0.27
P-tau$_{10\ pg/mL}$	0.88	(0.60, 1.27)	0.49	0.88	(0.61, 1.27)	0.49
CSF alpha-synuclein/total tau	0.99	(0.97, 1.01)	0.38	0.99	(0.96, 1.01)	0.39
Total tau/Aβ1-42	3.64	(0.02, 794.9)	0.64	4.46	(0.01, 999.9)	0.62
Phosphorylated tau-181/Aβ1-42	1.57	(0.01, 999.9)	0.92	0.97	(0.01, 999.9)	0.99
Phosphorylated tau-181/total tau	0.88	(0.20, 3.94)	0.87	0.88	(0.19,4.02)	0.86

[a] Model adjusted for age, gender, education, duration, Movement Disorder Society-Unified Parkinson's Disease Rating Scale part 3 motor score, and Geriatric Depression Scale

by neuropsychological testing. This finding is consistent with findings from the Norwegian ParkWest study, which reported an association between lower levels of CSF Aβ1-42 and cognitive deficits in the domain of memory [8], and later development of PD dementia [9]. It is also consistent with studies of more advanced PD cohorts associating lower CSF Aβ1-42 with development of dementia [4, 7, 18].

That lower CSF Aβ1-42 among medication-naïve early PD cases predicts CI 2 years later argues that the neuropathological process that leads to cognitive impairment in these cases may have started before or in parallel to motor symptom onset. However, the neuropathological correlates of lower CSF Aβ1-42 are not clear. In AD, it is hypothesized that low CSF Aβ1-42 may reflect higher levels of aggregation of Aβ protein in the cortex, signifying a more advanced neurodegenerative process [19–21]. Whether those with low levels of CSF Aβ1-42 may represent a subset of PD with coincident AD remains to be seen and may be elucidated with further follow-up (including postmortem neuropathological evaluation) [22, 23].

Strengths of the present study include finding a robust relationship between CSF markers and CI in a multicenter longitudinal study including a large sample size of participants with newly diagnosed PD without CI. Limitations include a definition of CI dependent only on neuropsychological test scores without assessment of participant's functional impairment [24], which was not available at time of participant enrollment. Taken together, this study provides evidence that CSF Aβ1-42 may play a role in prediction of early cognitive impairment among persons with newly diagnosed PD with mild motor symptoms. Early identification of markers of cognitive impairment is important for determining which patients may benefit most from therapies once they become available. Further longitudinal analysis following changes in CSF Aβ1-42 as they relate to cognition can be the next step in exploring the role of CSF Aβ1-42 in predicting cognitive impairment and dementia.

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References

1. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003) Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 60:387–392
2. Hughes TA, Ross HF, Musa S, et al. (2000) A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology 54:1596–1602
3. Mollenhauer B, Trenkwalder C, von Ahsen N, et al. (2006) Beta-amlyoid 1-42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia. Dement Geriatr Cogn Disord 22: 200–208
4. Parnetti L, Castrioto A, Chiasserini D, et al. (2013) Cerebrospinal fluid biomarkers in Parkinson disease. Nat Rev Neurol 9:131–140
5. Siderowf A, Xie SX, Hurtig H, et al. (2010) CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease. Neurology 75: 1055–1061
6. Montine TJ, Shi M, Quinn JF, et al. (2010) CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment. Mov Disord 25: 2682–2685
7. Parnetti L, Farotti L, Eusebi P, et al. (2014) Differential role of CSF alpha-synuclein species, tau, and Abeta42 in Parkinson's disease. Front Aging Neurosci 6:53
8. Alves G, Bronnick K, Aarsland D, et al. (2010) CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study. J Neurol Neurosurg Psychiatry 81:1080–1086
9. Alves G, Lange J, Blennow K, et al. (2014) CSF Abeta42 predicts early-onset dementia in Parkinson disease. Neurology 82: 1784–1790
10. Parkinson Progression Marker I (2011) The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 95:629–635
11. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. (2013) Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol 70:1277–1287
12. Vanderploeg RD, Schinka JA, Jones T, Small BJ, Graves AB, Mortimer JA (2000) Elderly norms for the Hopkins Verbal Learning Test-Revised. Clin Neuropsychol 14:318–324
13. Mitrushina MN (2005) Handbook of normative data for neuropsychological assessment, 2nd edn. Oxford University Press, New York
14. Groth-Marnat G (2009) Handbook of psychological assessment, 5th edn. John Wiley & Sons, Inc., Hoboken
15. Tombaugh TN, Kozak J, Rees L (1999) Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol 14:167–177
16. Sheridan LK, Fitzgerald HE, Adams KM, et al. (2006) Normative Symbol Digit Modalities Test performance in a community-based sample. Arch Clin Neuropsychol 21:23–28
17. Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Mov Disord 2015;In press.
18. Compta Y, Pereira JB, Rios J, et al. (2013) Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. Parkinsonism Relat Disord 19:717–724
19. Strozyk D, Blennow K, White LR, Launer LJ (2003) CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology 60:652–656
20. Fagan AM, Mintun MA, Mach RH, et al. (2006) Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 59:512–519
21. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. (2011) Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. Acta Neuropathol 121:597–609
22. Burack MA, Hartlein J, Flores HP, Taylor-Reinwald L, Perlmutter JS, Cairns NJ (2010) In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 74:77–84
23. Hyman BT, Phelps CH, Beach TG, et al. (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 8:1–13
24. Litvan I, Goldman JG, Troster AI, et al. (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 27:349–356